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**Patentanmeldung Nr. | Patent application No. | Demande de brevet n°**

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Use of haloarylpyrazole in systemic control of acarid infestation on animals

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Title: Use of haloarylpyrazole in systemic control of acarid infestation on animals

The present invention relates to the use of a specific haloarylpyrazole compound as active ingredient in the manufacture of a medicament for the systemic control of acarid infestation on animals.

Ticks are important blood feeding arthropod parasites that belong together with mites (Family: *Psoroptidae*) to the order *Acarina*. There are two well-established families of ticks, the *Ixodidae* (hard ticks), and *Argasidae* (soft ticks).
The *Ixodidae* species is of most economic importance and include the important species *Boophilus* spp., *Rhipicephalus* spp, *Ixodes* spp, *Hyalomma* spp., *Amblyomma* spp. and *Dermacentor* spp. Acarid infestation, i.e. infestation by ticks and mites can cause in livestock significant economic loss in the form of poor quality hide, wool or sheep skin, poor quality meat /tissue, reduced weight gain and even death as a result of the animal carrying ticks.

Ticks produce injury after infestation of animals in three respects: direct damage caused by parasitism such as local injury and blood loss; by toxins injected by the parasites and by the transmission of diseases including: anaplasmosis, tularaemia, Lyme disease, Q fever, Rocky Mountain spotted fever, and ehrlichioses and babesioses (piroplasmoses) of various animals.

Many mites also are intermediate hosts of diseases transmissible to humans, domesticated animals, and crops. Others are parasites as a result of their biting or feeding habits.

Safe, effective ways to eliminate these acarid parasites are desired both for the prevention of losses in livestock as well as for companion animal's well being and for well being and the comfort of its human associate. Treatments currently available achieve varying degree of success.

Thus, there continues to be a need for compounds and combinations thereof which can be used as active agents against acarid parasites, especially ticks or mites which afflict domestic animals and which are effective at low application rates, selective in biologic action and have low toxicity.

In EP 412849 certain aryl-1,2,3 triazoles and arylpyrazoles are disclosed in which the imidazol(in)e group is attached directly or indirectly through its 2-position to the triazole or pyrazole ring that have pesticidal activity. For certain of the compounds disclosed in EP 412849 systemic activity against ectoparasitic insects after oral application to an animal is described.

The invention proposes to improve the processes for controlling acarid parasites, especially ticks and mites in animals, especially in companion animals, in particular dogs.

It has been found that a particular compound mentioned in EP412849, 5-chloro-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-(4,5-dicyano-1H-imidazol-2-yl-3-methyl-1-H pyrazole, herein referred to as compound 22c, is effective against ticks when systemically applied.

The invention thus relates to the use of 5-chloro-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-(4,5-dicyano-1H-imidazol-2-yl-3-methyl-1-H pyrazole as active ingredient in the manufacture of a medicament for the systemic control of acarid infestation on animals.

The compound preferably is formulated to be administered systemically. Systemic administration is the administration of the composition to an animal at a site remote from the site where the parasite resides, e.g. by mouth, by injection, implant or by other means, for example transdermally by spot-on or pour-on, so that there is sufficient of the agent in the tissues or body fluids to kill the parasite feeding on the animal. With "systemic control of acarid infestation" is thus meant the control of acarids on an animal by systemically administering an antiparasitic composition.

The active ingredient is preferably administered in an oral formulation. The term "oral formulation" means that active ingredients are formulated into a product or formulation suitable for administering to the animal via the mouth. These products or formulations include, but are not limited to tablets, capsules, liquids, gels, pastes, oral sprays, buccal formulations, powders, granules, chewable treats or animal feeds containing the active ingredient. Generally such formulations include pharmaceutically acceptable auxiliaries. Such carriers are well known in the veterinary art.

Oral solid dosage forms are known in the art and described in, for example standard textbooks such as Remington: The science and Practice of Pharmacy, 20th Edition (2000), Chapter 45. Conventional tablets generally comprise the active ingredients and a diluent to assist in increasing the powder mass to a convenient size and improve compressability, a binder to hold the compressed powder together and a lubricant to assist in densification and ejection from the tablet die. They may also contain a disintegrate, to improve disintegration and dissolution as well as stabilizers, colours and flavours. Tablets are often coated to improve appearance or taste or to alter the dissolution properties. Tablets can be designed to dissolve fast or slow, and

depending on the actual volume and compressability of the drug, large or small. They can be made chewable or to dissolve under the tongue or in the pouch of the cheek.

Conventional liquid formulations are usually solutions, suspension or emulsions of the active ingredient together with suitable diluents, solvents, flavours and colours to form a palatable dosage form.

In general, an effective amount of the active ingredient, meaning a non-toxic but sufficient amount to provide the desired therapeutic effect is used. An appropriate "effective" amount in any individual case may be determined by a person skilled in the art using routine experimentation and may depend on the weight, age, and condition of the animal.
Preferably the treatment is carried out so as to administer to the animal a dose from 0.1 to 100 mg/kg bodyweight (bw) and in particular from 1 to 30 mg /kg bw, more preferably between 1-10mg/kg bw, of the compound 22c.

The compound 22c can be administered to all species of animals that have tick infestation. The recipient of the composition may be a livestock animal e.g. sheep, cattle, pig, goat, a laboratory test animal, e.g. guinea pig, rat or mouse or, in particular, a companion animal e.g. dog, cat rabbit or horse.

EXAMPLES:

Example 1: Treatment of tick infested dogs with compound 22c.

Two groups of 6 dogs were infested with ticks (*Rhipicephalus sanguineus* and *Ixodes ricinus*) before and at different time points after treatment. Group I was treated orally with Compound 22c at a dose of 4 mg/kg bodyweight (bw) followed by 3 weekly doses of 2 mg/kg bw. Group II remained untreated as positive control.
The parasite burden of individual dogs was assessed 48 h, 72 h or 120 h after infestation by removing and counting of ticks. Ticks were classed according to vitality (dead/alive) and the parasitic status of ticks (engorged/unfed; attached/free).

MATERIALS AND METHODS

**Study animals**

| | |
|---|---|
| Species: | Domestic dog |
| Number: | 12 |

Health status: The dogs were healthy at the start of the study as determined by a veterinarian on Day –2. None of the dogs had been treated with an acaricide/insecticide for at least 8 weeks prior to the study.
Identification: Ear and chip number

**Animal Housing**

Study animals were kept indoors in individual pens with concrete floors and a special resting area allowing the collection of parasites from the environment. The study was carried out according to the existing guidelines for the "Testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats" (EMEA/CVMP/005/00) providing maximum comfort to the dogs under study conditions.

**Parasite Infestation**

Dogs were experimentally infested with laboratory strains of *Rhipicephalus sanguineus* (50–100 unfed adults; sex ratio 1:1) and *Ixodes ricinus* (20 adult females) as reflected in table 1. Ticks were directly applied onto the back of the animal. For the time of parasite distribution over the host the dogs were kept quiet by sedation. Ticks of *Rhipicephalus sanguineus* were infested on day –2, day +5, day +12, day +16, and day +23. Because of limited availability *Ixodes ricinus* was infested prior to the first treatment (day –2) and in the last week of the study (day +23).

**Product specifications**

| | | |
|---|---|---|
| Investigational Product | | Compound 22c Tablet |
| Active Ingredient: | | Compound 22c (Ch. HT7a 99.1 %) 10.0 % (w/w) |
| Dosage | : | 4 mg/kg bodyweight -initial dose; 2 mg/kg bodyweight - maintenance dose |
| Application | : | Per os |

**Treatment**

Treatments followed the schedule as set out below:

| Day | Number of dogs | Investigational veterinary product | Dose | Application |
|---|---|---|---|---|
| 0 | 6 | Compound 22c | 4 mg/kg bw | Per os |
| +7 | 6 | Compound 22c | 2 mg/kg bw | Per os |
| +14 | 6 | Compound 22c | 2 mg/kg bw | Per os |
| +21 | 6 | Compound 22c | 2 mg/kg bw | Per os |

**Route and Method of Administration**

The investigational product was applied directly to the back of the tongue to induce swallowing. To calculate the doses body weights were used. The smallest unit that had been used was half a tablet. Tablets were not scored but were broken into even pieces. Where necessary the dose was rounded to the nearest half tablet. The administered doses were recorded.

**Assessments: Evaluation of Tick Numbers**

Each assessment started with the dogs of the treatment group to prevent cross-contamination of treated dogs with ticks of the control group.

Tick assessments on the dogs were made on the day +2, day +7, day +14, day +21 and day +23. Tick counts were made 48 hours after the first treatment and 48 hours, 72 hours or 120 hours after each re-infestation. For counting all ticks were removed from the animals and grouped into the following categories:

| Category | General findings | Attachment status | Effect |
|---|---|---|---|
| 1 | live | Free | no |
| 2 | live | attached – unengorged | no (except single ticks) |
| 3 | live | attached – engorged | no (except single ticks) |
| 4 | killed | Free | yes |
| 5 | killed | attached – unengorged | yes |
| 6 | killed | attached – engorged | no (except single ticks) |

**Calculation of Efficacy**

Efficacy calculation was based on the arithmetic means of number of ticks on treated dogs compared to the control group. For calculation of efficacy (%), the following formula (according to Abbot's formula) is used:

Efficacy = $100 \times (m_c - m_t)/m_c$

Control group ($m_c$): mean number of live ticks on the host animal

Treatment group ($m_t$): mean number of live (category 1-3) or killed, engorged ticks (category 6) on the host animal

**RESULTS**

The overall efficacy is given in figure 1.

Overall, the acaricide Compound 22c has an additive prophylactic activity against ticks preventing attachment (repellence).

Against *Rhipicephalus sanguineus* initial efficacy of 94 % was reached within 48 hours after the first treatment. Challenge infestations 48 hours after dosing (day 16; day 23) were controlled in the range of 98 - 99 %. Ticks infested 120 hours after the last dosing (day 5; day 12) were controlled with 93 - 95 %. For *Rhipicephalus sanguinues*, therapeutic tick control was achieved throughout the study (28 days)

with the weekly dosing schedule. Moreover, significant numbers of live but visibly damaged ticks were collected from the pens of treated dogs after each infestation indicating ticks failed to firmly attach to the host. Under natural challenge conditions this will be seen as a preventive effect against ticks. In conclusion, Compound 22c was highly efficacious against *Rhipicephalus sanguineus*.

Against *Ixodes ricinus* initial efficacy of 82 % was reached within 48 hours after the first treatment. A challenge infestation 48 hours after the last dosing (day 23) was controlled with 88 %. This indicates a significant efficacy against this tick species.

Overall, Compound 22c applied at a weekly dose was well tolerated and demonstrated an exceptional acaricidal potential.

CLAIMS:

1) Use of 5-chloro-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-(4,5-dicyano-1H-imidazol-2-yl-3-methyl-1-H pyrazole as active ingredient in the manufacture of a medicament for the systemic control of acarid infestation on animals.
2) Use according to claim 1, wherein the medicament is a formulation for systemic application.
3) Use according to claim 1 or 2, wherein the medicament is a formulation for oral application.
4) Use according to any of claims 1-3, wherein the animal is a companion animal.
5) Use according to any of claims 1-4,wherein the medicament is intended to be applied at a dose between 0.1 and 100 mg/ kg body weight of the animal.
6) Use according to any of claim 5, wherein the medicament is intended to be applied at a dose between 1 and 30 mg/ kg body weight of the animal.
7) Use according to any of claims 1-6, wherein the medicament comprises additionally pharmaceutically acceptable auxiliaries.

ABSTRACT:

The present invention relates to the use of 5-chloro-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-(4,5-dicyano-1H-imidazol-2-yl-3-methyl-1-H pyrazole as active ingredient in the manufacture of a medicament for the systemic control of acarid infestation on animals.
The compound preferably is formulated to be administered systemically.

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FIGURE 1: Efficacy of compound 22c against ticks.